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The associations between metabolic variables and NT-proBNP are blunted at pathological ranges: The Multi-Ethnic Study of Atherosclerosis

Otto A. Sanchez[d,*], Daniel A. Duprez[a], Hossein Bahrami[b], Lori B. Daniels[c], Aaron R. Folsom[d], Joao A. Lima[e], Alan Maisel[f], Carmen A. Peralta[g], David R. Jacobs Jr.[h]

[a] Division of Cardiology, University of Minnesota
[b] Stanford University
[c] School of Medicine, University of California, San Diego
[d] School of Public Health, Division of Epidemiology & Community Health, University of Minnesota
[e] Division of Cardiology, Johns Hopkins Bayview Medical Center
[f] School of Medicine, University of California, San Diego
[g] School of Medicine, University of California San Francisco
[h] School of Public Health, Division of Epidemiology & Community Health, University of Minnesota and University of Oslo

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ABSTRACT

Objective. Under physiological conditions brain natriuretic peptide (BNP) is inversely associated with metabolic risk factors, but under pathological conditions these associations may tend to plateau.

Material and methods. 5597 individuals in the Multi-Ethnic Study of Atherosclerosis (MESA), 45–84 years of age, free of overt cardiovascular disease in 2000–02 and then again in 2003–05 participated in this study. Associations between NT-proBNP and BMI, blood lipids, homeostasis model of insulin resistance (HOMA-IR) using linear regression models were adjusted for age, race, sex, BMI, % of energy from saturated fats, intentional exercise, statin use, antihypertensive medication use, diabetes and glomerular filtration rate. The inflection points (IP) at which these associations became nonlinear were determined using linear splines with knots at different levels of NT-proBNP.

Results. Participants with NT-proBNP ≥100 pg/mL (29%) tended to be older, on statins and anti-hypertensive medications vs. those with NT-proBNP <100 pg/mL. The IP point varies among variables and ranged from 50–120 pg/mL. NT-proBNP < IP, associated inversely with BMI, total cholesterol (TC), LDL-C, triglycerides (TG) and HOMA-IR, but positively with HDL-C. A higher proportion of participants with NT-proBNP ≥100 pg/mL had subclinical CVD.

Abbreviations: BMI, body mass index; CAC, coronary artery calcium; cIMT, common carotid intima media thickness; CT, computed tomography; CVD, cardiovascular disease; eGFR, estimate glomerular filtration rate; HDL-C, high density lipoprotein cholesterol; HOMA-IR, homeostasis model of insulin resistance; IL-6, interleukin-6; IP, inflection point; IR, insulin resistance; LDL-C, low density lipoprotein cholesterol; MESA, Multi-Ethnic Study of Atherosclerosis NT-proBNP, N-terminal-pro-brain natriuretic peptide; TC, total cholesterol; triglycerides, TG.

* *Corresponding author at:* School of Public Health, Division of Epidemiology & Community Health, University of Minnesota, West Bank Office Building 1300 South, Second Street, Suite 300, Minneapolis, MN 55454–1015. Tel.: +1 612 624 1573; fax: +1 612 624 0315.
E-mail address: sanc0050@umn.edu (O.A. Sanchez).

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All associations with NT-proBNP plateaued when NT-proBNP ≥ IP. Baseline level in NT-proBNP was not associated with 3-year change in BMI, TG, HDL-C or fasting glucose.

Conclusions. In a large cardiovascular disease-free cohort, NT-proBNP within the lower (physiological) range was inversely associated with TC, LDL-C, TG and insulin resistance with different inflection points, but at higher (pathological) levels these associations were blunted.

1. Introduction

Elevated levels of the amino-terminal-probrain natriuretic peptide (NT-proBNP) and BNP are well-known for increasing the risk of morbidity and mortality from cardiovascular diseases (CVD) [1,2]. Paradoxically, low levels of NT-proBNP are more frequent in obese, those with elevated triglyceride levels [3,4] and NT-proBNP is predictive of type 2 diabetes [5]. All of these variables are important risk factors in the development of CVD. Thus, NT-proBNP concentrations appear to have pathological implications at both low and high values.

In the absence of pathological influences, blood levels of NT-proBNP fluctuate in response to physiological variations in blood volume and pressure load in the heart [6] in an age and gender dependent manner [7,8]. Under this condition, BMI, blood lipids and insulin resistance (IR) have been shown to have an inverse association with NT-proBNP [3]. However, the presence of cardiovascular and inflammatory pathologies can substantially increase NT-proBNP [9,10] and induce a state of hypo-responsiveness to natriuretic peptides [11]. A state of hypo-responsiveness to natriuretic peptides would make it possible that the inverse association between NT-proBNP and BMI, blood lipids and IR seen under physiologic conditions would be lost when pathologic influences predominate. Whether this supposition is true is currently not known.

Previous reports on the association between NT-proBNP and BMI, blood lipids and fasting glucose have been obtained from cross sectional studies. Unfortunately, longitudinal studies which would lend further support for a cause and effect relationship have not been reported. The Multi-Ethnic Study on Atherosclerosis (MESA) offers the opportunity to assess changes in BMI, blood lipids and fasting glucose as a function of baseline and change in NT-proBNP.

Therefore, we hypothesized that cross-sectionally in asymptomatic adults free of overt cardiovascular disease the inverse association between NT-proBNP and BMI, blood lipids and insulin resistance plateau at the higher levels of NT-proBNP. To study this hypothesis, we used linear spline models to determine the inflection point at which the linear association between NT-proBNP with BMI, blood lipids and insulin resistance is lost. In addition, we hypothesized that baseline NT-proBNP predicts the direction of change in BMI and TC, LDL-C, triglycerides (TG) and fasting glucose and that change in NT-proBNP will be associated with change in BMI, blood lipids and blood glucose.

2. Methods

2.1. Study Subjects

We studied participants in the Multi-Ethnic Study of Atherosclerosis (MESA) recruited in 2000–2002 and during their third visit in 2003–2005. They were initially free of self-reported overt cardiovascular disease and renal failure. Included here were those in whom NT-proBNP were assayed at baseline, n = 5597 of the 6814 total participants in MESA and n = 4694 during the third visit. Details of study recruitment and design have been previously published [12].

2.2. Blood measurements

Blood lipids, insulin, and glucose were measured in blood samples following a 12 hour fast and sent to (Collaborative Studies Clinical Laboratory at Fairview University Medical Center, Minneapolis, Minnesota). Serum glucose and insulin were measured by the Vitros analyzer (Johnson & Johnson Clinical Diagnostics, Rochester, New York) and by a radioimmunoassay method using the Linco Human Insulin Specific RIA kit (Linco Research, St. Charles, MO), respectively. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated according to [13]. TG, total cholesterol (TC), and high density lipoprotein cholesterol (HDL-C) concentrations were measured using the cholesterol oxidase method (Roche Diagnostics, Indianapolis, IN) and low density lipoprotein cholesterol (LDL-C) was estimated according to [14]. NT-proBNP was measured at the VA San Diego Health Care System, using an ElecSys 2010 analyzer (Roche Diagnostics, Indianapolis, IN) with intra-assay and interassay coefficients of variation of 1.3% and 4.8%, respectively [15]. Serum creatinine levels were used to estimate glomerular filtration rate (eGFR) according to Chronic Kidney Disease-EPI (CKD Epidemiology Collaboration) equations [16]. IL-6 concentrations were measured by ultrasensitive enzyme-linked immunosorbent assay (Quantikine HS human IL-6 immunoassay; R&D Systems, Minneapolis, MN). NT-proBNP, height, weight, and blood lipids were remeasured at visit 3, but IL-6 and insulin were not measured then.

2.3. Covariates

All study covariates in the cross-sectional analyses were obtained from the MESA baseline clinical examination and assessed using standard protocols, as previously reported [17]. Common carotid intima media thickness (cIMT) was assessed at the common carotid artery as described previously [18]. Coronary artery calcium (CAC) was determined with electron beam or helical computed tomography (CT) as described in [19]. Left ventricular dimensions were determined using cardiac MR images according to [20]. Presence of plaque was defined by a >25% diameter narrowing in the common carotid artery [21]. Antihypertensive medication use was based on names of reported medication use/pill bottle examination. Left ventricular hypertrophy (LVH) was defined as a left ventricular mass in mg corrected by height in cm above the 95th percentiles by